516,352

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

29 NOV 2004

(43) International Publication Date
18 December 2003 (18.12.2003)

PCT

(10) International Publication Number
WO 03/103569 A2

(51) International Patent Classification[7]: A61K

(21) International Application Number: PCT/US02/17720

(22) International Filing Date: 4 June 2002 (04.06.2002)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant *(for all designated States except US)*: **ZILA INC.** [US/US]; 5227 North Seventh Street, Phoenix, AZ 85014-2800 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **OKOLOTOWICZ, Karl** [US/US]; 2343 West Main Street, No.1090, Messa, AZ 85201 (US).

(74) Agent: **DUCKWORTH, David, G.**; Drummond & Duckworth, 5000 Birch Street, Suite 400, East Tower, Newport Beach, CA 92660 (US).

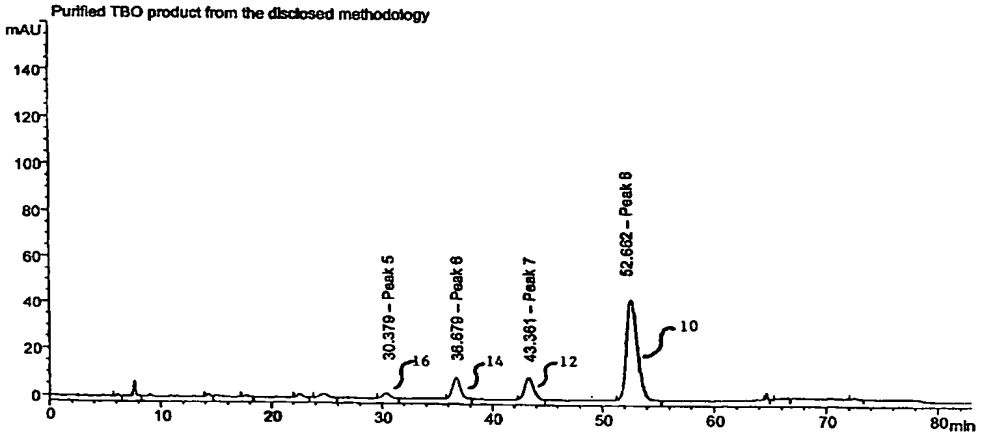
(81) Designated States *(national)*: AU, BR, CN, CZ, HU, IL, IN, JP, KR, MX, NO, NZ, PL, RU, SG, SK, US.

(84) Designated States *(regional)*: European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) **Title:** TOLUIDINE BLUE O DRUG SUBSTANCE AND USE THEREOF FOR IN VIVO STAINING AND CHEMOTHERAPEUTIC TREATMENT OF DYSPLASTIC TISSUES



(57) **Abstract:** The invention comprises an improved process for preparing TBO drug products includes the steps: (1) synthesising an indamine; (2) converting said indamine into an S-indaminyl thiosulfate; and (3) adding an oxidizing catalyst agent, complexing agent, and an acid to said S-indaminyl thiosulfate to formulate TBO and C-4-methyl regioisomer, and derivatives thereof. The invention further comprises new compositions of matter that are useful for detecting dysplastic tissue, as well as, treating dysplastic tissue, namely, TBO products predominantly comprised of peaks eight, peak six, or a combination thereof. *N,N*-dimenthyl-*p*-phenylenediamine as a starting material results in a TBO product composition comprised of peaks eight, seven, six, and five in the approximate ratios 33:5:5:1, respectively. Whereas *N*-dimethyl-*p*-phenylenediamine as a starting material results in a TBO demetylated product composition comprised of peaks six, five, tree and two in the approximate ratio 33:5:5:1, respectively. The invention further comprises an improved PLC method for analyzing the improved TBO drug product, the improvement comprising the addition of an ion-pairing reagent in a first mobile phase and forming a second mobile phase composition comprising 5o% alcohol by volume.

WO 03/103569 A2